

**From:** [Ravi Subramaniam](#)  
**To:** [KennyCrump@email.com](mailto:KennyCrump@email.com)  
**Subject:** human files  
**Date:** 05/12/2011 02:02 PM

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Kenny:

I have uploaded the (human model) zipped folder that I had originally downloaded from Environ's ftp site to google docs. Here is the link (you would not need to sign in). I sent it about half an hour ago but I find that the mailer has set it aside for sending only after 9 pm when data traffic will be low. So you will get it by mail as well later.

[https://docs.google.com/leaf?id=0B4KZCFTB-S-9ZDZkZGFzGUtOTAzNi00ZTNILWJlZDMtOGExNGQ3MDI5&hl=en&authkey=CNSP9\\_wP](https://docs.google.com/leaf?id=0B4KZCFTB-S-9ZDZkZGFzGUtOTAzNi00ZTNILWJlZDMtOGExNGQ3MDI5&hl=en&authkey=CNSP9_wP)

If you need the instructions as well, here is the link where it has been uploaded to.

[https://docs.google.com/leaf?id=0B4KZCFTB-S-9NTkwOGExMDQtMmU0My00Njk5LWFhYTgtZDgxZWExYWNhM2Y4&hl=en&authkey=CMm1g\\_wH](https://docs.google.com/leaf?id=0B4KZCFTB-S-9NTkwOGExMDQtMmU0My00Njk5LWFhYTgtZDgxZWExYWNhM2Y4&hl=en&authkey=CMm1g_wH)

*Ravi*

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Ravi Subramaniam  
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▼ "Kenny Crump" ---05/12/2011 12:39:22 PM---Ravi, I have been looking at doing the additional analyses we discussed. I have

From: "Kenny Crump" <[KennyCrump@email.com](mailto:KennyCrump@email.com)>  
To: Ravi Subramaniam/DC/USEPA/US@EPA  
Date: 05/12/2011 12:39 PM  
Subject: RE: your perspective on NRC review

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Ravi,

I have been looking at doing the additional analyses we discussed. I have reproduced the hockey stick analyses and the J-shape mod 1 analysis but am having trouble with the J-shape Mod 2 analysis. Perhaps I am not using the latest program. Do you have a copy of the human model that you could send to me?

Kenny S. Crump  
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(b) (6)

**From:** Kenny Crump [mailto:KennyCrump@email.com]  
**Sent:** Thursday, May 12, 2011 7:05 AM  
**To:** 'Subramaniam.Ravi@epamail.epa.gov'  
**Subject:** RE: your perspective on NRC review

Ravi,

Regarding the Journal of Toxicology, how about asking them if they would be willing to publish our EHP paper with an addendum that deals with the NRC review? The EHP paper is very relevant to the special issue and contains basically all we (speaking for myself at least) would like to say regarding the general question of utility of BBDR models for risk assessment. The addendum would be an added value that should be very timely and interesting to the readers of the journal. I have had papers published in multiple journals in the past. What do you think?

Kenny

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**From:** Subramaniam.Ravi@epamail.epa.gov  
[mailto:Subramaniam.Ravi@epamail.epa.gov]  
**Sent:** Monday, May 09, 2011 9:05 AM  
**To:** dhattis@(b) (6) Gary.Ginsberg@po.state.ct.us  
**Cc:** KennyCrump@email.com; White.Paul@epamail.epa.gov  
**Subject:** Re: your perspective on NRC review

Hi Gary and Dale:

Thank you for taking the time to give us your reading on this issue. We have been buried in this for too long and therefore prone to be highly biased, but so have the critics. Therefore your perspectives are very important to us. We will write a short clarifying paper shortly which also incorporates what you have suggested and send it around to you both.

Best Regards,

*Ravi*

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-----dhattis@aol.com wrote: -----

To: Ravi Subramaniam/DC/USEPA/US@EPA,

[Gary.Ginsberg@po.state.ct.us](mailto:Gary.Ginsberg@po.state.ct.us)

From: [dhattis\(b\)\(6\)](mailto:dhattis(b)(6)@aol.com)

Date: 05/06/2011 10:55AM

Cc: Paul White/DC/USEPA/US@EPA, [KennyCrump@email.com](mailto:KennyCrump@email.com)

Subject: Re: your perspective on NRC review

Dear Ravi and Kenny,

I have now read the NRC comments in both the summary and Chapter 3. The attached annotated sections of the report contain my detailed responses and suggestions in italics. Briefly, I think the NRC report can be fairly criticized for failing to appreciate the strength of the argument that the reversibility of formaldehyde-reactant reactions requires that inhaled formaldehyde is transmitted extensively in the body at some rate, and there is no justification to adopt an implicit null hypothesis of no transmission in the absence of experimental detection of some excess above the inevitable noise by existing imperfect measurement methods. I also think it was probably unnecessary (and perhaps impolitic) for the IRIS document to make an outright rejection of the BBDR modeling framework at low doses on grounds of uncertainty. Instead, although challenging, I think you can use your extensive sensitivity analyses as the starting point for a fair and balanced analysis of the range of "not clearly incorrect" values for incremental human risks for nasal, upper respiratory, and other cancers from low dose formaldehyde exposures. Such an analysis, evaluated by both likelihood and Bayesian subjective probability methods, could also yield useful information for juxtaposing likely economic and health effects of alternative regulatory control options.

I would be happy to contribute to such efforts, although in the light of other commitments I do not have an extensive amount of time to devote to this in the next several months.

Best wishes,

Dale

-----Original Message-----

From: Subramaniam.Ravi@epamail.epa.gov

To: Gary.Ginsberg@po.state.ct.us; DHattis (b) (6)

Cc: White.Paul@epamail.epa.gov; Kenny Crump <kennyCrump@email.com>

Sent: Wed, May 4, 2011 12:01 pm

Subject: your perspective on NRC review

Hi Dale and Gary:

You may know that the NRC completed its review of our formaldehyde IRIS assessment recently. It was very critical of our evaluation and use of the Conolly et al (CIIT) BBDR modeling and human extrapolation of the rat nasal tumor data in our assessment. We did use the CIIT BBDR model for rats to determine a point of departure based on an internal dose metric (formaldehyde flux) and then used the human computational fluid dynamics model to translate this POD to humans. In so doing, we had rejected their BBDR model for humans. We had carried out extensive uncertainty analysis which showed their human model as too uncertain to warrant replacing EPA's baseline approach. However the NRC opined that we should have used the the BBDR model for low dose human extrapolation, asserting that it was "one of the best-developed BBDR models to date".

We are in the process of revising the document in response to NRC suggestions. In the interim, we think a short paper that clarifies our uncertainty and sensitivity analysis further would help the process. We would very much appreciate your fresh perspective on our work if you can spare the time, and to see if there is mutual interest in collaborating on such a paper.

I am attaching the following: 1) NRC review summary (see page 4,5); 2) NRC Chapter 3 (see pages 31-45)-- this has their review of the BBDR use in more detail; 3) Crump et al. (2008)--our sensitivity analysis of Conolly human model; 4) Conolly et al. (2009)-- Rory's letter to the journal critiquing our paper.; 5) Crump et al. (2009)-- our rebuttal of Rory's letter

In addition there are two more papers which appeared in Risk Analysis and which detail the uncertainties further (Subramaniam et al. 2007, 2008). I can send these along if you need them.

The most significant uncertainty is the modeling of initiated cell birth and death rates for which there are no data. There are data (including that at low dose) for normal cell division rates, so Conolly et al. related initiated cell division rates to that of normal cells using a 2-parameter function. These parameters were determined by fitting the BBDR model predictions to the tumor incidence data in rats, and then assuming that the same function could be used for humans. Our sensitivity analysis of this issue showed that slight perturbations of these parameters (that were substantially smaller compared to the variability in the empirical normal cell division rates) could change human risk by more than 3-orders of magnitude, while not affecting the fit to the rat tumor incidence data in any appreciable way.

I will stop at this for now, and can continue further upon hearing from you.

(See attached file: NRC report Summary.docx) (See attached file: NRC Chap3.doc) (See attached file: Crump.Human.hchomodel.uncert\_AnnOccHyg.2008.pdf) (See attached file: ConollyLetter.on.Crump.AOH.2009.pdf) (See attached file: Crump.Reply.to.Conolly\_AOH.2009.pdf)

Best Regards,  
Ravi

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[attachment "dhcomNRC\_report\_Summary.docx" removed by Ravi Subramaniam/DC/USEPA/US]  
[attachment "dhcomNRC\_Chap3.doc" removed by Ravi Subramaniam/DC/USEPA/US]

